

U.S. HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM

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REVISED
JUSTIFICATION, TEST PLAN, AND ROBUST SUMMARIES

PHOSPHITE ISODECYL/PHENYL CHEMICAL CATEGORY:

Phosphorous acid, triisodecyl ester (CAS# 25448-25-3)
Phosphorous acid, diisodecyl phenyl ester (CAS# 25550-98-5)
Phosphorous acid, isodecyl diphenyl ester (CAS# 26544-23-0)
Phosphorous acid, triphenyl ester (CAS# 101-02-0)
Phosphorous acid, tris(methylphenyl) ester (CAS# 25586-42-9)

Prepared by:
Phosphite Producers HPV Consortium
and
Phosphite Manufacturers Consortium
1250 Connecticut Ave., N.W.,
Washington, D.C., 20036

Prepared for:
U.S. Environmental Protection Agency
Washington, D.C., USA

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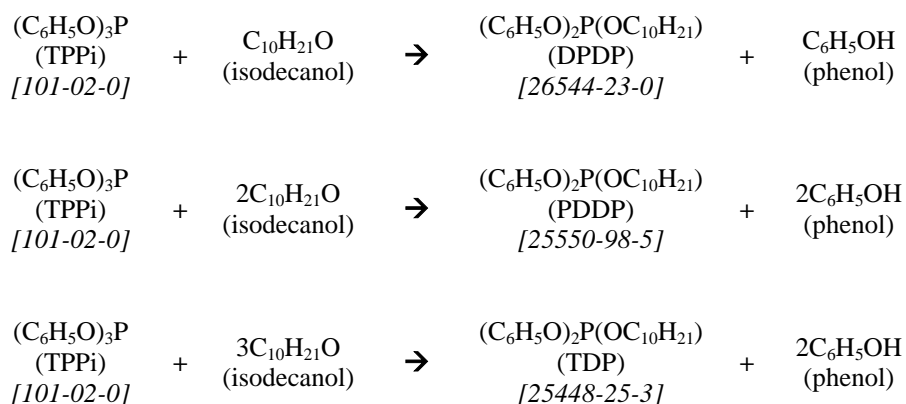
- Acute toxicity to fish, algae, and *Daphnia* – 2 of 5 compounds will be tested (combined with existing data on 2 compounds)
- *In vitro* Mammalian cell mutation assay - 2 of 5 compounds will be tested
- Biodegradation – 2 of 5 compounds will be tested (combined with existing data on 1 compound)

Manufacturing and Use Information

Manufacturing/Composition

The proposed category consists of phosphorous acid-tritolyl ester, phosphorous acid-triphenyl ester, as well as three products manufactured from triphenyl phosphite. Triphenyl phosphite and Tritolyl Phosphite are typically manufactured by reacting phosphorus trichloride with either phenol or cresol (mixture of m and p isomers) respectively. The isodecyl derivatives are manufactured from Triphenyl phosphite by reacting different mole ratios of isodecyl alcohol in sequence from phosphorous acid, isodecyl diphenyl ester to phosphorous acid, diisodecyl phenyl ester, and finally phosphorous acid, triisodecyl ester (Phenol is liberated as a by-product). The specific reactions are shown in Figure 1.

Figure 1: Manufacture



Transesterification reactions as described in Figure 1, however, are not specific. An outline of the possible reactions is shown in Figure 2.

Figure 2: Distribution of Transesterification Products

Starting with	$(\text{PhO})_3\text{P}$ “A”						
First molecule of alcohol	$(\text{PhO})_3\text{P}$ “A”	+	$(\text{PhO})_2\text{P}(\text{OR})$ “B”				
2 nd alcohol can react with either phosphite	$(\text{PhO})_3\text{P}$ “A”	+	$(\text{PhO})_2\text{P}(\text{OR})$ “B”	+	$(\text{PhO})\text{P}(\text{OR})_2$ “C”		
3 rd alcohol can react with any phosphite	$(\text{PhO})_3\text{P}$ “A”	+	$(\text{PhO})_2\text{P}(\text{OR})$ “B”	+	$(\text{PhO})\text{P}(\text{OR})_2$ “C”	+	$\text{P}(\text{OR})_3$ “D”

Transesterification of phenol with isodecanol to give triisodecyl phosphite from triphenyl phosphite (i.e., “A” to “D”) proceeds cleanly. Commercial triphenyl phosphite and triisodecyl phosphite are 98+% pure. However, for the partially transesterified products diphenylisodecyl

phosphite and phenyldiisodecyl phosphite, the reaction product obtained is actually a mixture of “A”, “B”, “C”, and “D” as shown in Figure 2. The ratio of each is controlled by the mole ratio of triphenyl phosphite and isodecanol reacted, and various other manufacturing conditions. It is not practical to produce pure diphenylisodecyl phosphite and phenyldiisodecyl phosphite. Diphenylisodecyl phosphite and phenyldiisodecyl phosphite sold in commerce typically range from 50-70% pure.

Commercially, tritolyl phosphite is also produced as major component (55-70%) in a triaryl phosphite reaction product, formed by reaction of phosphorus trichloride with m-cresol, p-cresol and phenol. The triaryl phosphite reaction product also contains monophenylditolyl phosphite, ditolylmonophenyl phosphite and triphenyl phosphite as minor constituents (tolyl = m and p isomers).

Degradation The most common form of degradation for phosphites is hydrolysis. Each of the phosphites in this category will hydrolyze to phosphorous acid and either phenol or isodecanol, or a mixture of both, depending on the amount of transesterification from aryl to alkyl phosphite. For tritolyl phosphite, the hydrolysis products are expected to be m-cresol and p-cresol. The expected hydrolysis products are shown in Figure 3.

Figure 3: Hydrolysis Products

Triisodecyl Phosphite 25448-25-3	Diisodecyl phenyl Phosphite 25550-98-5	Isodecyl phenyl Phosphite 26544-23-0	Triphenyl Phosphite 101-02-0	Tritolyl phosphite 25586-42-9
↓	↓		↓	↓
Phosphorous acid Isodecyl alcohol	Phosphorous acid Mixture of phenol and isodecyl alcohol		Phosphorous acid Phenol	Phosphorous acid Mixture of m-, p- cresol

Use

The triphenyl phosphite, diphenylisodecyl phosphite, phenyldiisodecyl phosphite and triisodecyl phosphite products are all secondary antioxidants used in polymer manufacture to improve color, processing, heat, and UV stability. These liquid phosphites are normally added to the polymer at 0.25-1.0% by weight to achieve the desired protection. Polymers that use these products include polyolefins, ABS, synthetic rubber, PVC, epoxies, polyurethanes, polyesters, and adhesives. Applications of polymers using these products are numerous. Diphenylisodecyl phosphite and phenyldiisodecyl phosphite are used primarily in non-food contact PVC applications as well as in polyurethanes. Triisodecyl phosphite is useful in many polymers and in lubricants where food-contact approval is not required. In addition to being a generally useful antioxidant for many polymers, triphenyl phosphite is also used in epoxy resin systems as a reactive diluent. The epoxy system is useful in such applications as adhesive coatings, laminates, potting and soldering compounds, and tooling. The Tritolyl phosphite product is primarily used as a ligand in the manufacture of a catalyst used in polyamide production.

Development of the Category

EPA has provided guidance on developing and justifying chemical categories:

- Develop a potential category by grouping a series of like chemicals.
- Gather published and unpublished literature on physicochemical characteristics and health and environmental effects.
- Evaluate the available data for adequacy.
- Construct a matrix of SIDS endpoints vs. category members arranged in order of the structural progression of the category.
- Evaluate the endpoints to determine whether data correlate with the structure.
- Make the category rationale and testing scheme available for review.
- Perform the testing.
- Add new data to the matrix and confirm that the data support the category rationale.

Category Definition As mentioned above, EPA has provided for the grouping of chemicals whose physicochemical and toxicological properties are likely to be similar or to follow a regular or predictable pattern. The category may be based on a common functional group, an incremental and constant change across the category, or common precursors and/or breakdown products. Data are extrapolated or interpolated to assess chemicals in the category rather than conducting additional testing on individual category members. If there is not sufficient existing information, the test plan for the category should include obtaining sufficient data to support the category.

We have already shown that the chemicals in this organophosphite category are manufactured from similar starting materials. Triphenyl phosphite and Tritolyl phosphite are both made by reacting phosphorus trichloride with the corresponding phenol or cresol isomers. The other Iso-decyl derivatives are made from Triphenyl phosphite by successive replacement of phenyl with iso-decyl groups. Therefore, these materials are linked by the common organophosphite functionality and by the common or closely related breakdown products (Figure 3). The category is also defined by the change of alkyl vs. aryl ester ratio as we move across the category and by the residual amount of triphenyl phosphite remaining in the product from the manufacturing process (Figure 4). It is postulated that differences in observed toxicity can be explained and predicted by these changes.

Figure 4: Incremental Changes

Product:	Triisodecyl Phosphite	Diisodecyl phenyl Phosphite	Isodecyl phenyl Phosphite	Triphenyl Phosphite
CAS RN	25448-25-3	25550-98-5	26544-23-0	101-02-0

Alkyl : Aryl ratio	3 : 0	1 : 2	1 : 2	0 : 3
% 101-02-0	0-2	0-5	20-30	100

Matrix of HPV Endpoints (Available Data)

To construct this matrix, existing data for all of the category chemicals were gathered and evaluated for adequacy. The results are shown in Tables 1-4.

Table 1: Summary of Physical and Chemical Data

← Increasing Alkyl : Aryl ratio						
Study Type		Triisodecyl Phosphite (25448-25-3)	Diisodecyl phenyl Phosphite (25550-98-5)	Isodecyl phenyl Phosphite (26544-23-0)	Triphenyl Phosphite (101-02-0)	Tritolyl phosphite (25586-42-9)
PHYSICAL AND CHEMICAL DATA						
1.0	Melting Point	No Data	No Data	No Data	No Data	52°C
2.0	Boiling Point	No Data	No Data	No Data	No Data	446 °C @ 1013 hPa* (EPIWIN)
3.0	Vapor Pressure	No Data	No Data	No Data	No Data	4.75 E-07 hPa at 25°C** (EPIWIN)
4.0	Partition Coefficient	No Data	No Data	No Data	No Data	8.3 at 25°C (EPIWIN)
5.0	Water Solubility	No Data	No Data	No Data	No Data	8.9 E-04 mg/l @ 25°C*** (EPIWIN)

→ Increasing TPPi content

* Available experimental boiling points at partial pressure are in accordance with the calculated value obtained with EPIWIN. Testing not necessary if estimated boiling point > 400 °C.

** Calculated value < 10⁻⁴ hPa at 25°C may be acceptable in lieu of measuring vapor pressure.

*** No testing is needed if water solubility value ≤ 1 µg/l.

Table 2: Summary of Environmental Fate & Pathway/Ecotoxicity Data

← Increasing Alkyl : Aryl ratio					
Study Type	Triisodecyl	Diisodecyl	Isodecyl phenyl	Triphenyl	Tritolyl

		Phosphite (25448-25-3)	phenyl Phosphite (25550-98-5)	Phosphite (26544-23-0)	Phosphite (101-02-0)	phosphite (25586-42-9)
ENVIRONMENTAL FATE & PATHWAY						
6.0	Photodegradation	No Data	No Data	No Data	No Data	$t_{1/2} = 0.78$ day (EPIWIN*)
7.0	Stability in Water	No Data	No Data	No Data	No Data	No data
8.0	Transport and Distribution	No Data	No Data	No Data	No Data	Soil and/or sediment (EPIWIN)
9.0	Biodegradation	No Data	Not Readily Biodegradable	No Data	No Data	No data
ECOTOXICITY						
10.0	Acute Toxicity to Fish (LC50: 96h)	No Data	> 100 mg/L (48h) (max. soluble conc.)	> 16 mg/L (max. soluble conc.)	No Data	No data
11.0	Acute Toxicity to Algae (LC50: 72h)	No Data	45 mg/L	1.6 mg/L	No Data	No data
12.0	Acute Toxicity to <i>Daphnia</i> (LC50: 48h)	No Data	0.2 mg/L	1 to 5 mg/L	No Data	No data

Increasing TPPi content



* calculated with AOPWIN, with 1.5×10^{-6} OH/cm³ and 12 h/d

Table 3: Summary of Toxicology Data

Increasing Alkyl : Aryl ratio



Study Type	Triisodecyl Phosphite	Diisodecyl phenyl Phosphite	Isodecyl phenyl Phosphite	Triphenyl Phosphite	Tritolyl phosphite
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		(25448-25-3)	(25550-98-5)	(26544-23-0)	(101-02-0)	(25586-42-9)
PHYSICAL AND CHEMICAL DATA						
13.1	Acute Toxicity (Oral)	> 5 g/kg	> 5 g/kg	4 g/kg	1.6 g/kg	11,000 mg/kg (Dupont, 1972, possibly based on only 1 rat per dose level)
13.2	Acute Toxicity (Dermal)	> 5 g/kg	> 5 g/kg	> 5 g/kg	> 2 g/kg but <5 g/kg	No data
13.3	Acute Toxicity (Inhalation)	> 12.6 mg/L (max. attainable conc.)	> 11.7 mg/L (max. attainable conc.)	> 8.4 mg/L (max. attainable conc.)	> 6.7 mg/L (max. attainable conc.)	No data
14.0	Genotoxicity <i>In Vitro</i> or <i>In Vivo</i> (Chromosome Aberration Tests)	Negative (Micronucleus Test)	Negative (Micronucleus Test)	Negative (Micronucleus Test)	Negative (Micronucleus Test)	No data
15.1	Genotoxicity <i>In Vitro</i> (Bacterial Test)	Not Mutagenic	Not Mutagenic	Not Mutagenic	Not Mutagenic	No data
15.2	Genotoxicity <i>In Vitro</i> (Mammalian Cells)	No Data	No Data	No Data	No Data	No data
16.0	Repeated Dose Toxicity	No Data	No Data	No Data	No Data	No data
17.0	Reproductive Toxicity	No Data	No Data	No Data	No Data	No data
18.0	Developmental Toxicity/ Teratogenicity	No Data	No Data	No Data	No Data	No data

Increasing TPPi content

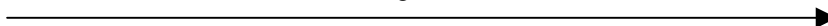
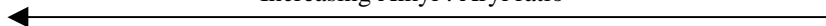


Table 4: Summary of Other Non-HPV Toxicology Data for Consideration

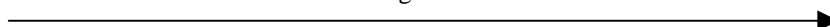
Increasing Alkyl : Aryl ratio



Study Type	Triisodecyl Phosphite	Diisodecyl phenyl Phosphite	Isodecyl phenyl Phosphite	Triphenyl Phosphite	Tritolyl phosphite
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	(25448-25-3)	(25550-98-5)	(26544-23-0)	(101-02-0)	(25586-42-9)
TOXICOLOGY – OTHER (NON-HPV) ENDPOINTS					
Primary Eye Irritation	Slight (Draize = 10.0/110)	Slight (Draize = 10.3/110)	Slight (Draize = 9.3/110)	Slight (Draize = 10.3/110)	No data
Primary Skin Irritation	Moderate (Draize = 5.4/8.0)	Moderate (Draize = 4.5/8.0)	Moderate (Draize = 4.6/8.0)	Moderate (Draize = 4.1/8.0)	Irritant (Dupont, 1972, not standard protocol)
Neurotoxicity	No Data	Weakly neurotoxic in hens	Weakly neurotoxic in hens	Highly neurotoxic in hens, rats and beagle dogs	Delayed neurotoxicity in hens and other species

Increasing TPPi content



Overview of Existing Test Results

Based on the information presented in Tables 2 and 3, there appears to be a clear progression of effects from less toxic to more toxic as the number of phenyl groups increase and concomitantly the number of isodecyl groups decreases; or alternately as the amount of triphenyl phosphite increases. For example, the acute aquatic toxicity values in fish and algae for the diisodecyl group ($LC_{50} > 100$ mg/L and $EC_{50} = 45$ mg/L, respectively) indicate a lower degree of toxicity compared to the monoisodecyl group ($LC_{50} > 16$ mg/L and $EC_{50} = 1.6$ mg/L, respectively). The 48-hour EC_{50} values in *Daphnia* were comparable for these two materials (0.2 mg/L and 1-5 mg/L, respectively). Due to the close chemical structure and physical-chemical properties of triphenyl phosphite and tritolyl phosphite, and the close physical chemical and environmental properties of their main degradation products (phenol and cresol, see table hereafter), tritolyl phosphite is expected to have the same pattern of eco-toxicity as triphenyl phosphite.

	Phenol* CAS 108-95-2	m/p-Cresol** CAS 1319-77-3
Melting Point	41°C	ca. 10°C
Boiling Point	182°C	ca. 200°C
Vapor Pressure	0.2 hPa @ 20°C	0.15 hPa at 25°C
Partition Coefficient	1.47	1.94 - 1.96
Water Solubility	84 g/l @ 20°C	24.4 g/l @ 25°C
Biodegradability	Readily biodegradable	Readily biodegradable
Fish 96h-LC50	5.02 mg/l	4.4 - 57.5 mg/l
Invertebrate 48h-EC50	3.1 mg/l	4.9 - >99.5 mg/l
Algae 72h-ErC50	61.1 mg/l	21 - 127 mg/l

* from SIAR Phenol, SIAM 19, 2004.

** from SIAR m/p-Cresol Category, SIAM 16, 2003.

For the mammalian toxicology end-points, the pattern of less toxic to more toxic is quite evident as the number of phenyl groups increases, or alternately as the triphenyl phosphite increases. The acute oral LD_{50} for both the tri- and diisodecyl materials is greater than 5 g/kg, whereas the monoisodecyl decreases to 4 g/kg and the pure triphenyl phosphite, the material without isodecyl

groups, is the most toxic at 1.6 mg/kg. A similar progression is evident for the acute dermal LD₅₀ as triphenyl phosphite is more toxic than the other compounds. Where all four materials respond similarly (e.g., *in vitro* bacterial tests and *in vivo* chromosome aberrations tests), the degree of toxicity is slight or totally absent (e.g., none of the four materials was genotoxic in either of the two test systems used). It is expected that tritolyl phosphite would have similar toxicity to triphenyl phosphite.

Although not a concern of the US EPA program, the pattern holds for other non-HPV mammalian and non-mammalian toxicology tests as well (Table 4). There was only very slight neurotoxicity in the hen assay with the di- and monoisodecyl materials, but the material without any isodecyl groups, triphenyl phosphite, was highly neurotoxic, not only to hens, but also to rats and dogs. Tritolyl phosphite is reported to have neurotoxic potential similar to triphenyl phosphite.

Robust summaries are available for each of the five compounds and are attached to this document (Appendix).

Proposed Testing Strategy

Based on the available information, these five materials appear to meet all of the criteria to be considered as a category. The testing scheme for the five materials is presented in Table 5 and outlined here.

Physical and Chemical Properties Data

PMC proposes to develop data on each of the four products for the following physical chemical properties:

- Melting Point
- Boiling Point
- Vapor Pressure
- Octanol/Water Partition Coefficient
- Water Solubility

For tritolyl phosphite, available experimental values and estimated values are adequate for purposes of the HPV Challenge program and therefore no further testing is proposed.

Environmental Fate and Effects

PMC proposes to develop data on each of the five products for the following:

- Photodegradation • Stability in Water
- Transport and Distribution

With regards to biodegradation, since adequate data exist for one of the interior products (PDDP), PMC proposes to test only the outer members of the category (TDP, TPP and TTPi).

Due to the close chemical structure and physical-chemical properties of triphenyl phosphite and tritolyl phosphite, and the close physical chemical and environmental properties of their main

degradation products (phenol and cresol), tritolyl phosphite is expected to have the same environmental fate properties as those of triphenyl phosphite as regards hydrolysis in water in environmentally relevant conditions and biodegradation.

Ecotoxicity

Since adequate data exists for the interior products (PDDP and DPDP), PMC proposes testing only the outer members of the category (TDP and TPP) for the following:

- Acute Toxicity to Fish
- Acute Toxicity to Algae
- Acute Toxicity to *Daphnia*

Due to the close chemical structure and physical-chemical properties of triphenyl phosphite and tritolyl phosphite, and the close physical chemical and environmental properties of their main degradation products (phenol and cresol), tritolyl phosphite is expected to have the same ecotoxicity properties as those of triphenyl phosphite.

Mammalian Toxicity

Adequate data exists for four of the five members of the category for acute oral, dermal, and inhalation toxicity, as well as for the Ames mutagenicity and *in vivo* chromosomal aberration assays. There is limited data for tritolyl phosphite. There are no data available for reproductive, developmental, or repeated dose toxicity for any of the five materials. PMC proposes testing for acute oral and dermal toxicity and an Ames test for tritolyl phosphite plus testing only the outer members (TDP and TPPi) of the category for the following:

- *In vitro* mammalian cell mutation assay
- Combined repeat dose, reproductive, and developmental toxicity

Test Plan Rationale

By testing the “two outside members” of the category, the toxicity of the “interior members” can be inferred if the two materials on the ends have similar toxic responses. For example, if there is no toxicity noted in a test with the triisodecyl and the “zero” isodecyl material (TPPi), then the mono- and diisodecyl materials would not be expected to exhibit any toxic effects in the same test. If the two end materials are significantly different (i.e., one produces a severe toxic effect and the other produces no toxic effect), then testing will be conducted on one or both of the interior materials, depending on the nature of the effects observed and the magnitude of the observed differences.

Testing Schedule

Based on this testing plan, we are rearranging our commitment to EPA for the order of testing to permit triphenyl phosphite and triisodecyl phosphite to begin testing in 2001. Any subsequent testing required because of significant differences in toxic responses would be conducted during the following year. Triisodecyl phosphite is currently scheduled for initiation of testing in 2002 and triphenyl phosphite is currently scheduled for testing beginning in 2003. The mono- and diisodecyl phosphites are scheduled for 2001. We would, therefore, propose to begin the testing for the triphenyl and triisodecyl phosphites upon approval of the category by EPA and the necessary 120-day posting period on the EPA HPV website for external comments. This would

move the start of testing, if needed, for the “interior” materials from 2001 to 2002.

The test program proposed for the new chemical added to the category, tritoly phosphite, will be commissioned following receipt of EPA’s comments on the testing proposal and inclusion in the category justification. The testing program for the original four members, based on the original testing plan (September 10th, 2001) and comments received from EPA and NGO’s, is currently in progress. The revised robust summaries for these substances will be updated and submitted following completion of the work.

Table 5: Proposed Test Plan for the Isodecyl/Phenyl Phosphite Category Members

		← Increasing Alkyl : Aryl ratio				
Study Type		Triisodecyl Phosphite (25448-25-3)	Diisodecyl phenyl Phosphite (25550-98-5)	Isodecyl phenyl Phosphite (26544-23-0)	Triphenyl Phosphite (101-02-0)	Tritolyl phosphite (25586-42-9)
1.0	Melting Point	TEST (OECD 102)	TEST	TEST	TEST	Adequate or estimated
2.0	Boiling Point	TEST (OECD 103)	TEST	TEST	TEST	
3.0	Vapor Pressure	TEST (Calculation)	TEST	TEST	TEST	
4.0	Partition Coefficient	TEST (OECD 107)	TEST	TEST	TEST	
5.0	Water Solubility	TEST (OECD 105)	TEST	TEST	TEST	
6.0	Photodegradation	TEST (Estimate)	TEST	TEST	TEST	Estimated
7.0	Stability in Water	TEST (OECD 111)	TEST	TEST	TEST	Testing not required by analogy with TPPi
8.0	Transport and Distribution	TEST (Fugacity Model*)	TEST	TEST	TEST	Estimated
9.0	Biodegradation	TEST (OECD 301F)	Adequate	Testing Not Required	TEST	Testing not required by analogy with TPPi
10.0	Acute Toxicity to Fish	TEST (OECD 203)	Adequate	Adequate	TEST	Testing not required by analogy with TPPi
11.0	Acute Toxicity to Algae	TEST (OECD 201)	Adequate	Adequate	TEST	
12.0	Acute Toxicity to <i>Daphnia</i>	TEST (OECD 202)	Adequate	Adequate	TEST	
13.1	Acute Oral Toxicity	Adequate	Adequate	Adequate	Adequate	TEST (OECD 423)
13.2	Acute Dermal Toxicity	Adequate	Adequate	Adequate	Adequate	TEST (OECD 402)
13.3	Acute Inhalation Toxicity	Adequate	Adequate	Adequate	Adequate	Testing not required by analogy with TPPi

Increasing Alkyl : Aryl ratio

Study Type		Triisodecyl Phosphite (25448-25-3)	Diisodecyl phenyl Phosphite (25550-98-5)	Isodecyl phenyl Phosphite (26544-23-0)	Triphenyl Phosphite (101-02-0)	Tritolyl phosphite (25586-42-9)
14.0	Chromosomal Aberration Assay	Adequate	Adequate	Adequate	Adequate	Test only if OECD 471 (Ames test) +ve
15.1	Mutagenicity (Ames - <i>In vitro</i> Bacterial Test)	Adequate	Adequate	Adequate	Adequate	TEST (OECD 471)
15.2	Mutagenicity (<i>In vitro</i> Mammalian Cell Mutation Assay)	TEST (OECD 476)	Testing Not Required	Testing Not Required	TEST	Test only if OECD 476 for TDPi or TPPi +ve
16.0 - 18.0	Combined Repeat Dose, Reproductive, and Developmental Toxicity	TEST (OECD 422)	Testing Not Required	Testing Not Required	TEST	Testing not required by analogy with TPPi

Increasing TPPi content

*: EQC Level III Fugacity Model

1: The test methods used for the TDP will be used for all compounds, where a TEST is indicated